

Inventors: John C. Reed  
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- B<sup>b</sup>  
*SUP E8  
cont*
85. (New) A method of modulating the level of apoptosis in a cell, comprising the steps of:
- introducing a nucleic acid molecule encoding a NAC functional fragment according to claim 86 into the cell; and
  - expressing said NAC functional fragment in said cell, wherein the expression of said NAC functional fragment modulates apoptosis in said cell.

86. (New) A functional fragment of the nucleic acid molecule of either claim 1 or claim 71, wherein said functional fragment comprises a nucleotide sequence encoding a NB-ARC domain corresponding to amino acids 329-547 of SEQ ID NO:2, and wherein said functional fragment associates with SEQ ID NO:2.

REMARKS

Claims 1, 2, 4-28 and 30-66 are pending. Claims 10, 12-17, 19-26, 28, 30-37 and 39-65 have been withdrawn from consideration as directed to a non-elected invention. By the amendments herein, claims 1, 4, 5, 6, 7, 8, 9, 11, 27 and 66 have been amended, claim 2 has been canceled, and new claims 67-85, directed to the elected subject matter, have been added. Accordingly, following entry of the amendments, claims 1, 4-28 and 30-85 will be pending, with claims 1, 4, 5, 6, 7, 8, 9, 11, 27 and 66-85 under examination. A marked-up copy of the claims showing the amendments is attached hereto as Appendix A.

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**APPENDIX A**

[FOR THE CONVENIENCE OF THE EXAMINER, THE PENDING CLAIMS AND NEW CLAIMS HAVE BEEN GROUPED TOGETHER BELOW ACCORDING TO SUBJECT MATTER]

1. (Amended) An isolated [Isolated] nucleic acid molecule encoding a NB-ARC and CARD containing protein (NAC), comprising a nucleotide sequence encoding a polypeptide having at least 80% identity to SEQ ID NO:4 or SEQ ID NO:6, or the complement of said nucleotide sequence,

wherein said polypeptide does not comprise amino acids 918-947 of SEQ ID NO:2, and

wherein said polypeptide associates with SEQ ID NO:2 or with Apaf-1 [, or complements thereof, selected from:

(a) DNA encoding the amino acid sequence set forth in SEQ ID NOs:2, 4 or 6, or

(b) DNA that hybridizes to the DNA of (a) under high stringency conditions, wherein said DNA encodes biologically active NAC, or

(c) DNA degenerate with respect to either (a) or (b) above, wherein said DNA encodes biologically active NAC.]

67. (New) The nucleic acid molecule of claim 1, comprising a nucleotide sequence encoding a polypeptide having at least 95% identity to SEQ ID NO:4 or 6.

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68. (New) The nucleic acid molecule of claim 1, comprising a nucleotide sequence encoding amino acids 1373-1473 of SEQ ID NO:2.

69. (New) The nucleic acid molecule of claim 1, comprising a nucleotide sequence encoding amino acids 329-547 of SEQ ID NO:2.

70. (New) The nucleic acid molecule of claim 1, comprising a nucleotide sequence encoding SEQ ID NO:4 or 6.

4. (Amended) A nucleic acid molecule according to claim 1, wherein the nucleotide sequence of said nucleic acid molecule is the same as that set forth in either [any] of SEQ ID NOs:3 or 5 [1, 3 and 5].

5. (Amended) The [A] nucleic acid molecule of [according to] either claim 1 or claim 71, wherein said nucleic acid molecule is cDNA.

6. (Amended) A vector containing the nucleic acid molecule of either claim 1 or claim 71.

7. (Amended) Recombinant cells containing the nucleic acid molecule of either claim 1 or claim 71.

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71. (New) An isolated nucleic acid molecule encoding a NAC, comprising a nucleotide sequence encoding a polypeptide having at least 80% identity to SEQ ID NO:2, or the complement of said nucleotide sequence,

wherein said polypeptide comprises amino acids 1262-1305 of SEQ ID NO:2, and

wherein said polypeptide associates with SEQ ID NO:2 or with Apaf-1.

72. (New) The nucleic acid molecule of claim 71, comprising a nucleotide sequence encoding a polypeptide having at least 95% identity to SEQ ID NO:2.

73. (New) The nucleic acid molecule of claim 71, comprising a nucleotide sequence encoding amino acids 1373-1473 of SEQ ID NO:2.

74. (New) The nucleic acid molecule of claim 71, comprising a nucleotide sequence encoding amino acids 329-547 of SEQ ID NO:2.

75. (New) The nucleic acid molecule of claim 71, comprising a nucleotide sequence encoding SEQ ID NO:2.

76. (New) The nucleic acid molecule of claim 71, wherein the nucleotide sequence of said nucleic acid molecule is the same as that set forth in SEQ ID NO:1.

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8. (Amended) An oligonucleotide comprising at least 30 contiguous [15] nucleotides up to 1035 contiguous nucleotides of **[capable of specifically hybridizing with a]** the nucleotide sequence set forth in any of SEQ ID Nos: 1, 3 and 5 or the complement of said nucleotide sequence.

77. (New) An oligonucleotide consisting of the nucleotide sequence set forth as nucleotides 985-1641 of SEQ ID NO:1 or its complement, or comprising at least 20 contiguous nucleotides therefrom.

78. (New) An oligonucleotide consisting of the nucleotide sequence set forth as nucleotides 2422-2844 of SEQ ID NO:1 or its complement, or comprising at least 20 contiguous nucleotides therefrom.

79. (New) An oligonucleotide consisting of the nucleotide sequence set forth as nucleotides 3235-3960 of SEQ ID NO:1 or its complement, or comprising at least 20 contiguous nucleotides therefrom.

80. (New) An oligonucleotide consisting of the nucleotide sequence set forth as nucleotides 2870-2959 of SEQ ID NO:1 or its complement, or comprising at least 20 contiguous nucleotides therefrom.

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81. (New) An oligonucleotide consisting of the nucleotide sequence set forth as nucleotides 4117-4419 of SEQ ID NO:1 or its complement, or comprising at least 20 contiguous nucleotides therefrom.

82. (New) An oligonucleotide comprising at least 20 contiguous nucleotides of the nucleotide sequence set forth as nucleotides 3784-3915 of SEQ ID NO:1 or its complement.

9. (Amended) **[An]** The oligonucleotide **[according to]** of any of claims 8, 77, 78, 79, 80, 81 or 82 **[claim 8]**, wherein said oligonucleotide is labeled with a detectable marker.

11. (Amended) A kit for detecting the presence of a **[the]** NAC nucleotide **[cDNA]** sequence comprising at least one oligonucleotide according to claim 9.

18. (Unamended) A method for expression of a NAC protein, said method comprising culturing cells of claim 7 under conditions suitable for expression of said NAC.

27. (Amended) A method for identifying nucleic acids encoding a mammalian NAC, said method comprising:

contacting a sample containing nucleic acids with the **[an]** oligonucleotide of any of claims 8, 77, 78, 79, 80, 81 or 82 **[according to claim 8]**, wherein said contacting is effected under high stringency hybridization conditions, and identifying compounds which hybridize thereto.

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38. (Unamended) A method of modulating the level of apoptosis in a cell, comprising the steps of:

- a) introducing a nucleic acid molecule encoding a NAC according to claim 1 into the cell; and
- b) expressing said NAC in said cell, wherein the expression of said NAC modulates apoptosis in said cell.

83. (New) A method of modulating the level of apoptosis in a cell, comprising the steps of:

- a) introducing a nucleic acid molecule encoding a NAC according to claim 71 into the cell; and
- b) expressing said NAC in said cell, wherein the expression of said NAC modulates apoptosis in said cell.

84. (New) A method of modulating the level of apoptosis in a cell, comprising the steps of:

- a) introducing a nucleic acid molecule encoding a NAC functional fragment according to claim 66 into the cell; and
- b) expressing said NAC functional fragment in said cell, wherein the expression of said NAC functional fragment modulates apoptosis in said cell.

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85. (New) A method of modulating the level of apoptosis in a cell, comprising the steps of:

- a) introducing a nucleic acid molecule encoding a NAC functional fragment according to claim 86 into the cell; and
- b) expressing said NAC functional fragment in said cell, wherein the expression of said NAC functional fragment modulates apoptosis in said cell.

66. (Amended) A functional fragment of the nucleic acid molecule of either **[aid according to]** claim 1 **or** claim 71, wherein said functional fragment comprises **a nucleotide sequence encoding [nucleic acid selected from the group consisting of nucleic acid encoding]** a CARD domain corresponding to amino acids 1373-1473 of SEQ ID NO:2, **and wherein said functional fragment associates with SEQ ID NO:2 or with Apaf-1 [and a NB-ARC domain corresponding to amino acids 329-547 of SEQ ID NO:2].**

86. (New) A functional fragment of the nucleic acid molecule of either claim 1 or claim 71, wherein said functional fragment comprises a nucleotide sequence encoding a NB-ARC domain corresponding to amino acids 329-547 of SEQ ID NO:2, and wherein said functional fragment associates with SEQ ID NO:2.

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The amendment to independent claim 1, new independent claim 71, and new dependent claims 67-70 and 72-75 are supported by claim 1 as filed, and also at page 18, lines 4-9, which recites NAC polypeptides having at least 80% or at least 95% identity to reference amino acid sequences; at page 21, lines 3-21 and Figure 1B, which describes the amino acid sequences present or absent in the various NAC isoforms; at page 18, lines 21-24, which describes a biological activity of an invention NAC as the ability to homo-oligomerize; at page 84, lines 16-19 and Figure 5A, which describes that invention NACs interact with Apaf-1; and at page 14, lines 15-18, which indicates that the term "associate" means that the NAC can bind to a protein relatively specifically to form a bound complex.

The amendment to claim 4 and new claim 76 are supported by claim 4 as filed. The amendment to claims 6 and 7 are supported by claim 6 and 7 as filed.

The amendment to claim 8 and new claims 77-82 are supported by claim 8 as filed and at page 34, lines 4-9, and at page 35, lines 13-20, which describes oligonucleotides of at least 20 or at least 30 nucleotides. New claim 77 is also supported at page 14, lines 4-7, which indicates that the NB-ARC domain of NAC corresponds to amino acid residues 329-547 of SEQ ID NO:2 (i.e. nucleotides 985-1641 of SEQ ID NO:1). New claim 78 is also supported at page 15, lines 28-31, which indicates that the LRR domain of NAC corresponds to amino acid residues 808-948 of SEQ ID NO:2 (i.e. nucleotides 2422-2844 of SEQ ID NO:1). New claim 79 is also supported at page 17, lines 4-7, which indicates that the TIM-Barrel-like domain of NAC corresponds to amino acid

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residues 1079-1320 of SEQ ID NO:2 (i.e. nucleotides 3235-3960 of SEQ ID NO:1). New claim 80 is also supported at page 12, lines 21-24, which indicates that the CARD domain of NAC corresponds to amino acid residues 1373-1473 (i.e. nucleotides 4117-4419 of SEQ ID NO:1). New claims 81 and 82 are also supported at page 21, lines 3-21, which indicates that alternatively spliced exons of NAC correspond to nucleotides 2870-2959 and nucleotides 2870-2959 of SEQ ID NO:1.

The amendments to claims 9 and 11 are supported by claims 8, 9 and 11 as filed. The amendment to claim 27 is supported by claims 8 and 27 as filed. New claims 83-85 are supported by claim 38 and claim 1 as filed. The amendment to claim 66 and new claim 86 are supported by claim 1 as filed.

As set forth above, the amendments and new claims are fully supported by the specification and do not introduce new matter. Accordingly, entry of the amendments and new claims is respectfully requested.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1, 2, 4-9, 11, 18, 27, 38 and 66 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking adequate written description and enablement. Claim 2 has been canceled. The rejection as it applies to claims 1, 4-9, 11, 18, 27, 38 and 66 is respectfully traversed for the reasons that follow.

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With regard to written description, the Office Action acknowledges that the specification discloses:

...isolated DNA encoding a biologically active NAC which hybridizes with high stringency to DNA consisting of SEQ ID NOS:1, 3 or 5, or DNA encoding the amino acid sequences set forth in SEQ ID NOS:2, 4 or 6, and functional fragments of those sequences.

However, the Action states that the specification does not provide sufficient guidance regarding:

...the nucleic acid or amino acid sequence characteristics of a NAC responsible for any type of biological activity.

or sufficiently describe:

...the effects of any nucleic acid or amino acid changes on any biological activity.

The Action further states that:

In the absence of any description of the biological activity of the encoded "NAC" proteins, the skilled person cannot envision the detailed chemical structure of the encompassed polynucleotides which may share those characteristics...

With regard to enablement, the Action acknowledges that the specification is enabling for:

...an isolated nucleic acid encoding an NB-ARC and CARD containing protein (NAC)

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selected from DNA consisting of SEQ ID Nos:1, 3 or 5, or DNA encoding the amino acid sequences set forth in SEQ ID Nos:2, 4 or 6, and oligonucleotides capable of hybridizing with SEQ ID Nos:1, 3, or 5.

However, it is alleged that the specification does not reasonably provide enablement for:

...functional fragments of the above, DNA encoding a biologically active NAC which hybridizes to the DNA molecules identified above with high stringency, or which is degenerate to those nucleic acid molecules, or for methods of modulating the levels of apoptosis in a cell by introducing the above identified sequences into the cell.

It is further alleged that the specification:

...does not provide any guidance as to any specific biological activity of the novel "NAC" proteins encoded by the disclosed cDNA or demonstrate that any of the disclosed proteins or protein domains or fragments have any apoptosis modulating activity either *in vitro* or *in vivo*.

As amended herein, claim 1, new claim 71, and their dependents are directed to nucleic acid molecules encoding polypeptides having at least 80% amino acid sequence identity to NAC $\beta$  (SEQ ID NO:2), NAC $\gamma$  (SEQ ID NO:4) or NAC $\delta$  (SEQ ID NO:6), or functional fragments thereof comprising the CARD or NB-ARC domains of NAC. As amended, these claims require that the encoded polypeptides have the biological activity of associating

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with SEQ ID NO:2 (NAC $\beta$ ) or with Apaf-1. Claim 38 and new claims 82-84 also require that the encoded polypeptide has the ability to modulate apoptosis when expressed in a cell.

As taught throughout the specification, the function of associating with a cellular NAC is mediated, independently, by the NAC CARD and the NAC NB-ARC domains, while the function of associating with Apaf-1 is mediated by the NAC CARD domain.

The specification teaches that a nucleic acid molecule encoding a polypeptide comprising a NAC CARD domain, with or without other residues of NAC outside of the CARD domain, will mediate association with NAC or Apaf-1 (page 78, lines 1-4; page 78, line 34 to page 79, line 17; page 80, line 33 to page 81, line 1; page 19, line 31 to page 20, line 4). Accordingly, the skilled person would reasonably expect that an invention NAC or functional fragment having extensive variations in the amino acid residues outside of the native CARD domain would result in a polypeptide that retains the ability to associate with NAC $\beta$  or Apaf-1 through its CARD domain.

The skilled person would also reasonably expect that certain of the residues within the NAC CARD domain could also be varied while retaining association with NAC $\beta$  or Apaf-1 through the CARD domain, while variation at other residues would abolish CARD:CARD association. For example, guided by the alignment of CARD domains shown in Figure 1E, and knowledge in the art of the structure of other CARD domains, the skilled person would predict that it would be important to retain the tertiary structure of the six alpha helices, and to retain other residues indicated to

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be highly conserved among CARDs, in order to retain NAC CARD domain function.

Likewise, the specification teaches that a polypeptide comprising a functional NAC NB-ARC domain, with or without other residues of NAC outside of the NB-ARC domain, will mediate association with NAC (page 82, lines 29-31; page 19, line 31 to page 20, line 4). Accordingly, the skilled person could reasonably expect that an invention NAC or functional fragment having extensive variations in the amino acid residues outside of the native NB-ARC domain would result in a polypeptide that retains the ability to associate with NAC $\beta$  through its NB-ARC domain.

The skilled person would also reasonably expect that certain of the residues within the NAC NB-ARC domain could be varied while retaining association with NAC $\beta$  through the NB-ARC domain, while variations of other residues would abolish NB-ARC:NB-ARC association. For example, the specification teaches that the nucleotide binding site of NB-ARC, such as the P-loop (see Figure 1D), kinase 2 motif and kinase 3a motif, are important for nucleotide binding and NB-ARC:NB-ARC association. A publication by van der Biezen et al., Curr. Biol., 8:R226-R227 (1998) is incorporated by reference, which describes these and other structural features conserved among NB-ARC domains.

Based on the teachings in the specification as to the NAC domains and the amino acid residues within these domains that are important for NAC or Apaf-1 association, as described above, the skilled person could predict with a reasonable amount of

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certainty whether a potential NAC or fragment associates with SEQ ID NO:2 or with Apaf-1. The skilled person could confirm this prediction, without undue experimentation, using one of the *in vitro* or *in vivo* assays taught in the specification for determining polypeptide association. For example, the specification teaches how to determine NAC association using *in vitro* GST pull-down assays (page 78, line 12, to page 79, line 17); yeast two-hybrid assays (page 79, line 19, to page 80, line 5); and mammalian cell co-transfection/co-immunoprecipitation assays (page 83, line 16, to page 84, line 32).

In view of the above amendments and remarks, it is respectfully submitted that the claimed NAC nucleic acid molecules and fragments are adequately described and enabled.

With respect to enablement for NAC nucleic acid molecules that modulate apoptosis, the specification further teaches that NAC nucleic acid molecules that associate with cellular CARD or NB-ARC containing polypeptides modulate apoptosis either positively or negatively. For example, the specification teaches that a dominant negative NAC that does not itself induce apoptosis may form hetero-oligomers with an apoptotic NAC, thus interfering with the apoptosis-inducing activity of NAC (page 15, lines 3-15). Thus, a dominant negative NAC can be, for example, a NAC fragment comprising only a CARD domain or a NB-ARC domain, or a full-length NAC with a non-functional CARD domain or a non-functional NB-ARC domain.

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As corroboration that a NAC or NAC fragment that associates with cellular NAC or with Apaf-1 modulates apoptosis, Applicants submit as Exhibit A a publication by Chu et al., J. Biol. Chem. 276:9329-9245 (2001). As shown in Figure 3B and 3D of Exhibit A, full-length NAC forms complexes with itself and with Apaf-1. As shown in Figure 4E of Exhibit A, recombinant expression of full-length NAC $\beta$  in HEK293 cells sensitizes these cells to suboptimal concentrations of inducers of apoptosis that act through the Apaf-1 pathway. As shown in Figure 4D of Exhibit A, overexpression of full-length NAC $\beta$  in combination with Apaf-1 and pro-Casp9 results in synergistic increases in induction of apoptosis.

In contrast, recombinant expression of a NAC fragment containing only the NAC CARD, which retains the ability to associate with NAC and with Apaf-1 (Figure 3A of Exhibit A), or containing only the NAC NB-ARC, which retains the ability to associate with NAC, has the opposite effect, namely interfering with apoptosis induced by Apaf-1/pro-Casp9 and by apoptotic inducers (Figure 4F of Exhibit A).

Therefore, Exhibit A corroborates that a NAC or NAC fragment that associates with either SEQ ID NO:2 or with Apaf-1 will modulate apoptosis either positively or negatively .

The Action further alleges that:

The specification does not provide sufficient guidance for introducing and expressing a "NAC" protein in cells *in vivo* such that the

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level of "NAC" expression results in any effect on apoptosis in the animal.

References by Marshall et al., Orkin et al. and Verma et al., are cited in support of an assertion that "at the time of filing" the art recognized the unpredictability of achieving therapeutic levels of gene expression *in vivo*. It is respectfully pointed out that the filing date of the instant application is October 1999, whereas the cited Marshall and Orkin publications date back to 1995 and the Verma publication dates back to 1997. Whereas Orkin perhaps could state in 1995 that "...many of the perceived advantages of vector systems have not been experimentally validated," and "[w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol...," as quoted in the Action, progress in the field of gene therapy with genes that modulate apoptosis was such that these statements clearly could not have been made four years later at the time of filing the instant application, as will be discussed further below.

At the time of filing the application, the skilled person, given the guidance in the specification, could readily have administered a claimed NAC nucleic acid molecule or fragment with an expectation of achieving sufficient levels of expression to modulate apoptosis. The specification teaches gene delivery using a variety of methods, including viral based delivery systems, such as adenoviral and retroviral vectors (page 56, line 24, to page 57, line 29); liposome encapsulated nucleic acid molecules (page 59, lines 12-17); and particle bombardment (page

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59, lines 17-21). The specification also teaches methods of targeting specific cell types using a tissue-specific vector or tissue-specific promoter or enhancer (page 57, line 30, to page 58, line 19), or by using receptor-mediated DNA delivery (page 59, lines 4-12). The specification further teaches appropriate routes of gene delivery, which include direct, local inoculation (page 59, line 26 to page 60, line 1), as well as systemic administration, such as by subcutaneous or intravenous routes (page 58, lines 29-34). Such gene delivery systems and methods were known in the art, at the time of filing, to be suitable for providing sufficiently high levels of expression of a gene that modulates apoptosis to have an effect *in vivo*.

As corroboration, attached hereto as Exhibit B is a publication by Roth et al., Oncology 13:148-154 (1999), which reviews clinical trials with the pro-apoptotic gene p53. Exhibit B describes the use of retroviral vectors to express either p53 or antisense ras in nude mice in sufficient amounts to mediate a therapeutic anti-tumor effect (page 149, column 3). Retroviral vectors were subsequently used in a human clinical trial with p53 to yield sufficient delivery of the gene to the tumor, and sufficient levels of gene expression, to induce apoptosis (page 152, columns 2-3).

Exhibit B also describes preclinical animal studies (page 150, columns 1-3) and human clinical trials (page 152, column 3, to page 153, column 1) using adenoviral vectors expressing p53 to successfully induce apoptosis of tumor cells. Notably, despite evidence of the induction of antibodies to the

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adenoviral vector after repeat inoculation, transgene expression continued to occur and clinical responses were maintained (page 153, column 1).

Accordingly, in view of the evidence of the clinical trials reported in Exhibit B, it is respectfully submitted that the "formidable challenges" referred to in the Verma et al. publication, in 1997, and quoted in the Action, relating to:

...the lack of efficient delivery systems,  
lack of sustained expression, and host immune reactions

had been successfully overcome in the art by the filing date of the instant application with regard to gene therapy with genes that modulate apoptosis.

Thus, in view of the teachings in the specification, the corroboration provided by Exhibit A regarding the ability of NACs and NAC fragments to modulate apoptosis, and the corroboration provided by Exhibit B of the state of the art at the time of filing the application regarding gene therapy with genes that modulate apoptosis, it is respectfully submitted that claims directed to methods of modulating apoptosis are enabled.

In view of the above amendments and remarks, reconsideration and removal of the rejection of claims 1, 2, 4-9, 11, 18, 27, 38 and 66 under 35 U.S.C. § 112, first paragraph, is respectfully requested.

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Rejections under 35 U.S.C. § 112, second paragraph

Claim 66 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite in view of the phrase "the nucleic acid aid according to claim 1." The typographical error in claim 66 has been corrected by the amendment herein to remove the term "aid." Accordingly, reconsideration and removal of the rejection of claim 66 under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Rejections under 35 U.S.C. § 102(a) or § 103 (a)

Claims 8, 9, 11 and 27 stand rejected under 35 U.S.C. § 102(a) as allegedly anticipated by Nagase et al., DNA Res. 6:63-70 (1999) or, in the alternative, under 35 U.S.C. § 103(a), as allegedly obvious over Nagase et al., DNA Res. 6:63-70 (1999). The rejection is respectfully traversed for the reasons that follow.

Nagase et al. (1999) is cited as describing cDNA clones having large regions of 100% sequence identity to SEQ ID NOS:1, 3 and 5, and the use of RT-PCR ELISA for identifying the expression pattern of cDNAs. It is acknowledged that Nagase et al. (1999) does not disclose the characteristics of the oligonucleotides used in the RT-PCR ELISA assay. The Action refers to a second publication (Nagase et al. DNA Res. 5:277-286 (1998)), referenced in Nagase et al. (1999), that generally describes the use of digoxigenin-labeled 21mer primers in RT-PCR ELISA, and which indicates that HUGE database sequence primers are available on the internet at [www.kazusa.or.jp](http://www.kazusa.or.jp). The Office Action has not

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provided any evidence that the sequence of any 21mer primers from SEQ ID NOS:1, 3 and 5 suitable for RT-PCR ELISA were disclosed at [www.kazusa.or.jp](http://www.kazusa.or.jp) or elsewhere in the art prior to the filing date of the application.

The Action alleges that the description of the Nagase et al. primers and their use in detecting mRNA expression in cells anticipates claims 8, 9, 11 and 27. In the alternative, the Action alleges that in view of the cited references it would have been obvious to use 21mer oligonucleotides labeled with (DIG)-11-dUTP to identify SEQ ID NOS:1, 3 and 5 using RT-PCR ELISA.

As amended herein, claim 8 requires that the oligonucleotide comprise at least 30 nucleotides up to 1035 nucleotides of SEQ ID NOS:1, 3 or 5, or of the complement thereto. The description of 21mer oligomers in Nagase et al. (1999), Nagase et al. (1998) and/or [www.kazusa.or.jp](http://www.kazusa.or.jp), provides no teaching or suggestion of oligonucleotides comprising at least 30 nucleotides up to 1035 nucleotides of SEQ ID NOS:1, 3 or 5. Therefore, it respectfully submitted that the cited reference does not anticipate, and the cited references in combination do not render obvious, claims 8, 9, 11 or 27.

In view of the above amendments and remarks, reconsideration and removal of the rejections of claims 8, 9, 11 and 27 under 35 U.S.C. § 102 and/or 35 U.S.C. § 103 are respectfully requested.

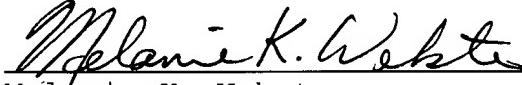
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**CONCLUSION**

In light of the Amendments and Remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, she is invited to call Cathryn Campbell or the undersigned agent.

Respectfully submitted,

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